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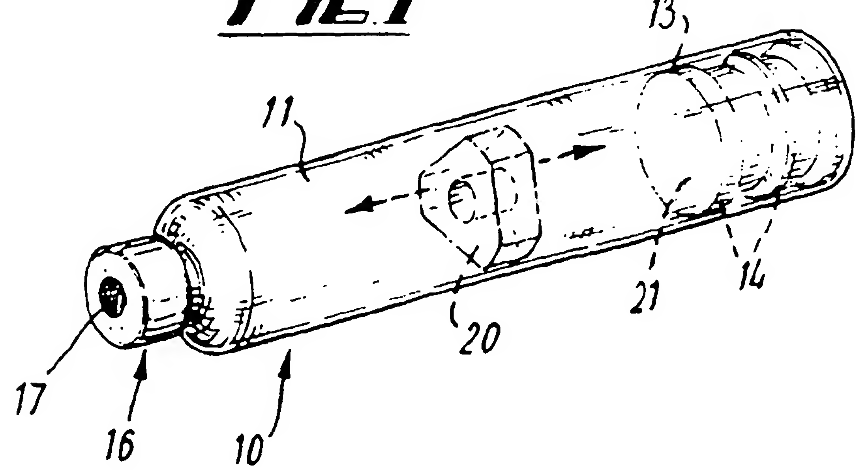
(54) Containers for liquid medicaments

(57) A container 10 for a liquid medicament suspension, e.g. an insulin crystal suspension, has a tube 11 with a sealing piston 13, a cap 16, and a mixing element 20 which moves along the tube 11 to assist mixing the suspension. The element 20 is guided by the inner surface of the tube 11 and has restricted lateral movement but is free to move axially for example by tilting or end to end inversion of the container. Flow passages such as apertures and peripheral recesses are provided in the mixing element which can serve to promote turbulent flow.

The containers are particularly suited for use as multi-dose cartridges for pen-like injection devices or for portable infusion devices which have piston- operating mechanisms to co-operate with the container piston.

FIG.1



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lateral movement is to[illegible]e. but it should not be so great as to enable the [illegible]g element to move significantly out of axial alignment with the container with the undesired result that the element is free to tumble and roll as the container is tilted or inverted or. indeed. to tilt itself out of alignment with the container wall and thereby risk becoming trapped or wedged within the container so that its mixing function is compromised. The mixing element can, however. be free to rotate axially and it may be shaped appropriately to promote or reduce such rotary movement as it slidingly moves within the container.

This is one important difference between the mixing element employed in the present invention and the mixing elements proposed and used in the prior art. i.e. the movement of the element within the container is primarily a sliding movement along the length of the container (optionally with an axial rotary action). rather than being primarily a rolling or tumbling action as in the prior art. Further, and as is preferred. the mixing element of the present invention extends, at least in part, across essentially the full diameter of the container. with the result that a greater proportion of the cross-section of the container is subjected to the sweeping and mixing action of the element as it moves from one end of the container to the other.

The shaping of the mixing element. to permit flow of suspension from one side to the other. suitably takes the form of one or more apertures through the element or, additionally or alternatively, one or more passages defined by the mixing element in combination with the inner surface of the container, such as by recesses or channels formed in the periphery of the mixing element. These apertures. recesses or channels may. if desired. be profiled. e.g. with projections or constrictions. to increase turbulence in the suspension as it flows from either side of the mixing element to the other. and/or they may be angularly disposed relative to the axis of the mixing element and relative to its direction of travel so as to impart an axial rotary motion to the element as it moves axially within the container. Additionally or alternatively. the mixing element may be provided with vanes. e.g. radially disposed vanes. angled with respect to the axis of movement of the element. The vanes may be angled all in the same orientation. so as to cause or promote the mixing element to develop a rotational movement as it moves axially within the container. or may be arranged in opposing orientation to increase turbulence in the flow of the suspension medium as it flows between the vanes.

Where the mixing element is to be caused to move axially within the container by the simple action of tilting or end to end inversion of the latter. the material from which the element is made should have a density sufficiently different from that of the suspension medium. preferably at least a 10% difference. more preferably at least a 50% difference and most preferably at least a 100% difference. to enable the element to fall or rise as the container is so manipulated. Suitable materials which are more dense include metals. such as stainless steel. ceramics. certain plastics and glass. especially sintered glass. Materials less dense than the suspension medium. and which would be buoyant therein. include. for example. certain foamed plastics. Alternatively. the mixing element can be hollow and gas. e.g. air. filled and thereby achieve buoyancy in the suspension medium. Further. the mixing element can be formed of or have implanted therein a magnetic or magnetic responsive material so that the axial movement of the element is caused and controlled by the movement of a correspondingly magnetic device external to the container. such as a slidable collar. e.g. forming a part of any pen-like body in which the container in use is housed. Where the mixing element is magnetic or magnetically responsive. its overall density is less relevant. The material from which the element is made. or at least that part in contact with the suspension medium. should. however. be pharmaceutically acceptable. that is to say be non-toxic and inert to the suspension components.

The material from which the container body is formed is preferably glass, although other pharmaceutically acceptable materials include metals. such as aluminium. rigid plastics materials and ceramics.

The invention may be performed in various ways. and several specific embodiments with possible modifications will now be described by way of example only, with reference to the accompanying drawings. in which :-

Fig. 1 is a perspective view of a cylindrical cartridge or ampoule for a liquid medicament suspension and constructed in accordance with the invention:

Fig. 1A is a part-section of the outlet of the cartridge of Fig. 1:

Fig. 2 is an end view of the mixing element:

Fig. 3 is a section through the mixing element of Fig. 2:

Fig. 4 is a perspective view of the mixing element of Fig. 2:

Figs. 5 to 10 are end views of various differently shaped mixing elements:

Figs 5A to 10A are sections respectively on the lines 5-5. 6-6. 7-7. 8-8. 9-9 and 10-10 of Figs. 5 to 10·

(s) are equally applica[illegible] mixing elements having different peripheral shap[illegible]g. as described below.

A selection of other examples of mixing elements is shown in Figs. 5 to 10.

In Figs. 5 and 5A. the mixing element 40 has a single central aperture 34 and eight angularly spaced-apart periphery portions 31 presented on radially disposed teeth 41 having flat sides 42 the angle between adjacent sides 42 of neighbouring teeth being 60°. In one specific example, the surface portions 31 are on a diameter of 9.3mm. for use in a cartridge with an inner diameter of 9.5mm.

In Figs. 6 and 6A. the mixing element 43 is similar to mixing element 40 but has two equal sized apertures 44. each of 2mm diameter.

The mixing element shown in Figs. 7 and 7A is provided with four generally rectangular channels or slots 45 equiangularly spaced around the periphery and which, when the element is located within a cylindrical container. serve to define. with the inner wall surface of the container. passages to allow flow of the suspension from either side of the element to the other. Between the channels or slots 45 are four equiangular periphery portions with surfaces arranged to co-operate with the inner surface of the container. Typically, the channels or slots are 1mm deep. The element is also shown with a single central aperture. but that may be omitted or replaced by two or more apertures.

The element 46 in Figs. 8 and 8A is similar to that in Figs. 7 and 7A, but the channels are more numerous and each extends over a greater radial arc, with the result that the peripheral portions take on the form of radially disposed teeth 47. Element 46 has a single central aperture therethrough.

The mixing element of Figs. 9 and 9A is similar to that of Figs. 8 and 8A. but is provided with two apertures 44. Although these apertures are shown as having straight bores. the bores may, as described above, be tapered. either in the same or in opposing directions.

The mixing element illustrated in Figs. 10 and 10A presents three angularly spaced-apart surfaces shaped to co-operate with the inner surface of a tube shaped container. in similar manner to the surfaces 31 of the mixing element 20 shown in Figs. 1 to 4. but instead of being separated by flats the co-operating surfaces are separated by part-circular peripheral cut-outs 48. for example of radius 1.5mm.

The mixing element 50 shown in Fig.11 although presenting a plurality of peripheral surfaces to co-operate with the inner surface of a cylindrical cartridge. has deep slots 51 cut into the periphery and which run parallel to the axis of the element and its direction of travel. Fig. 12 shows a similar mixing element but where the slots. although individually straight, are inclined to the central axis of the element and to its direction of travel so as to induce a rotational motion to the element as it moves axially within the cartridge and through the suspension.

This rotational motion is a characteristic of the mixing element examples shown in Figs. 13 to 15A. The mixing elements of Figs. 13 and 14 are of a general cup or dish shape. having a base part 60 and a rim which presents a peripheral outer continuous surface 61 to co-operate with the inner surface of a cylindrical cartridge container. Angularly spaced portions are removed from the base 60 to provide apertures therein. and inner and outer radial slits 63. 64 are cut in the base to enable portions 65 to be bent inwards away from the plane of the base 60. The angular extent of portions 65 can vary, as can the number of such portions - see Fig. 14 - and as can also the angle to which the portions are bent from the plane of base 60. The base 60 is connected to an axial tube 66. which defines a central aperture 34

The mixing element shown in Figs. 15 and 15A is similar to that shown in Fig. 12 with channels 70 whose side faces 71 are inclined at an angle to the axis of the mixing element so that axial movement of the element within the liquid medicament container produces a rotation of the element about its axis. The number of channels and their angle of inclination can be varied.

Figs. 16 and 17 show further turbulence-inducing arrangements within a mixing element. In these embodiments. the mixing elements comprise inner and outer co-axial tubular members, 80 and 81, connected by angularly spaced vanes 82. In Fig. 16. two sets of vanes are shown, one set being both axially and radially displaced from the other. The vanes 82 can be arranged so that their planes are parallel to the axis of tubes 80 and 81 or. if it is desired to induce a rotational movement to the element as it traverses the container. they may be disposed at an angle thereto, in propeller fashion. In order to increase turbulence in the liquid medicament as the element passes. the vanes 82 in each set as shown in Fig. 16 may be disposed at an angle to those in the other set, e.g. at an equal but opposite angle to the axis of the tubes 80 and 81.

It is desirable that the medicament suspension be homogenised to an acceptable degree by the minimum number of passing traverses of the mixing element along the container length. e.g. by tilting or end to end inversion movements of the container. Ideally. one or two tilting movements would be required: that is to say. if the cartridge has been stored in a horizontal position. it is desirable that a single tilting in one sense to 45°. accompanied by one full pass of the mixing element in one direction. should produce a suspension of acceptable homogeneity. or, failing that. that a second full pass by reverse tilting the container through 90° should suffice. The desirability of this ease in bringing the suspension into homogeneity is so that patients or users who inadvertently forget to follow the instructions to invert the cartridge/pen a set number of times will in any event by their handling of the device and preparing to use it e.g. by simply removing the device from a pocket. handbag or carrying case and positioning it for injection. e.g. into a thigh perform sufficient tilting and like manipulative movements with the device as to cause an acceptable level of homoge-

TABLE 1 (continued)

TEST No	Mixing Element	Number of Cartridge Inversions/Tilts	Average Degree of Homogenisation
3a	3x 2.0mm. steel balls	20	Incomplete. max 40%
3a	Element of invention	2	Complete.100%
4a	3x 2.0mm. steel balls	20	Incomplete. max 50%
4a	Element of invention	3	Complete.100%

COMPARATIVE EXAMPLE 2

In this Example. commercially available 3ml. Insulin Protamin HM Penfil cartridges (suspension). from Novo-Nordisk. were used. again of standard 6.5 cm length and 9.5mm internal diameter. Half were tested as supplied commercially. that is to say containing a conventional mixing element in the form of a glass bead having a diameter of 2.5mm. and the other half were modified by removal of the glass bead and replacement with a mixing element according to the invention. as used in Comparative Example 1. above.

Tests 1b to 4b were then carried out in identical manner to Tests 1a to 4a. above. there again being 3 cartridges in each batch tested. and again the average degree of homogenisation was visually assessed and the number of inversions/tilts noted. The results are set out in the following Table 2.

TABLE 2

TEST No.	Mixing Element	Number of Cartridge Inversions/Tilts	Average Degree of Homogenisation
1b	1x 2.5mm.glass bead	20	Incomplete. max 50-60%
1b	Element of Invention	3	Complete 100%
2b	1x 2.5mm.glass bead	20	Incomplete. max 50-60%
2b	Element of Invention	3	Complete 100%
3b	1x 2 5mm.glass bead	20	Incomplete. max 50-60%
3b	Element of Invention	3	Complete 100%
4b	1x 2.5mm.glass bead	20	Incomplete. max 50-60%
4b	Element of Invention	3	Complete 100%

Claims

1. A container for a liquid medicament suspension having a piston operable therein and an outlet therefrom. and containing a solid mixing element, characterised in that the mixing element and the inner surface of the container are shaped to co-operate and constrain the mixing element against significant lateral movement but permit axial movement. the mixing element being shaped to permit flow of suspension from either side of the element to the other as the element moves axially.

2. A container as claimed in claim 1. characterised in that the mixing element is shaped so as to present a continuous or discontinuous peripheral surface co-operating with the inner surface of the container.

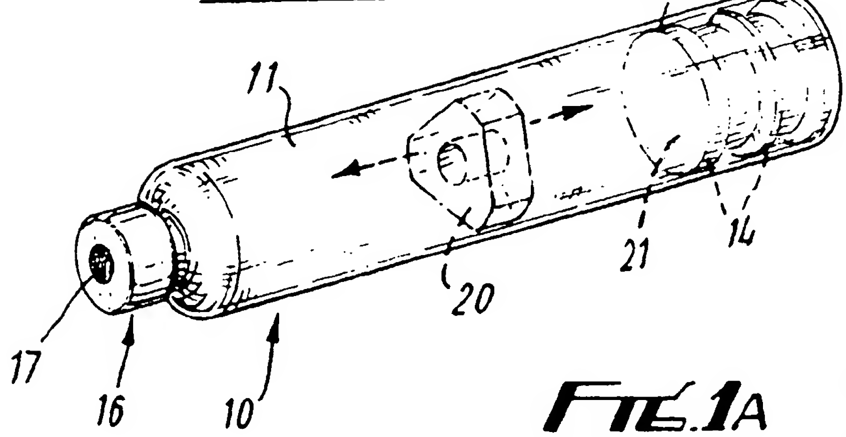
3. A container as claimed in claim 1. characterised in that the mixing element is shaped so as to present and define a plurality of angularly spaced-apart regions for co-operation with the inner surface of the container.

4. A container as claimed in claim 1. 2 or 3. characterised in that the mixing element is constrained against significant lateral movement within the container by being dimensioned so as to be in a close but sliding fit within the container.

5. A container as claimed in any preceding claim characterised in that the mixing element is free to rotate axially.

6. A container as claimed in any preceding claim characterised in that the mixing element. in order to permit flow of suspension from either side of the element to the other. is provided with one or more apertures through the element.

FIG.1



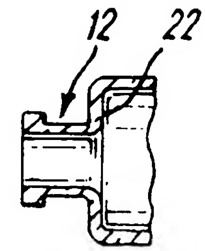
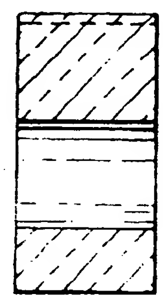


FIG.1A

FIG.3



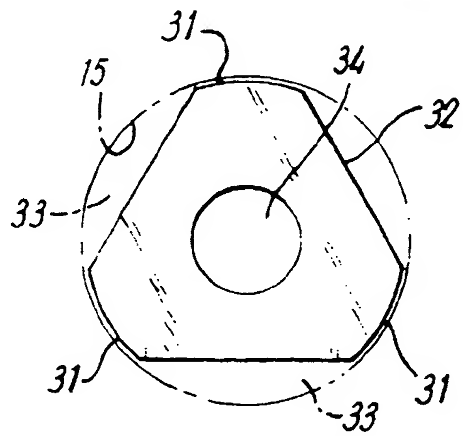


FIG.2

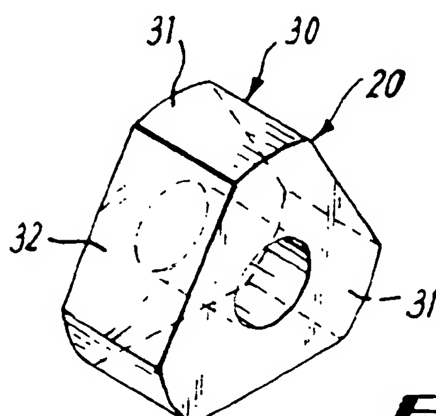


FIG.4

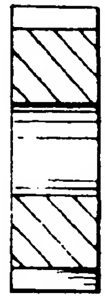


FIG. 8A

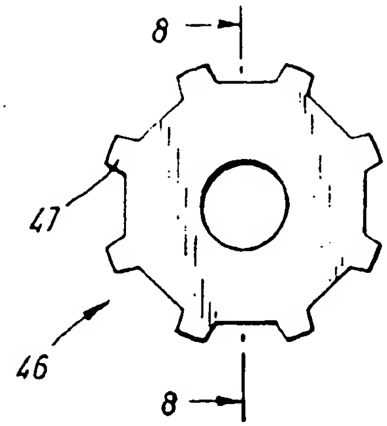


FIG. 8

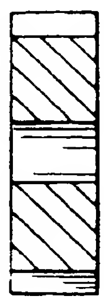


FIG. 9A

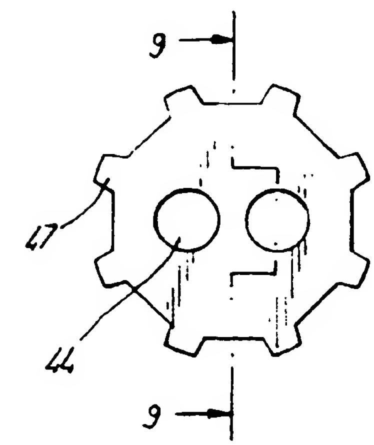


FIG. 9

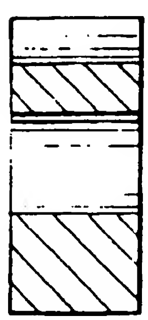


FIG. 10A

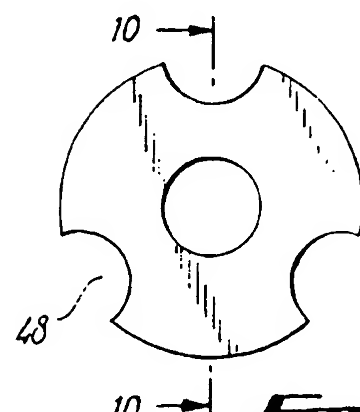


FIG. 10

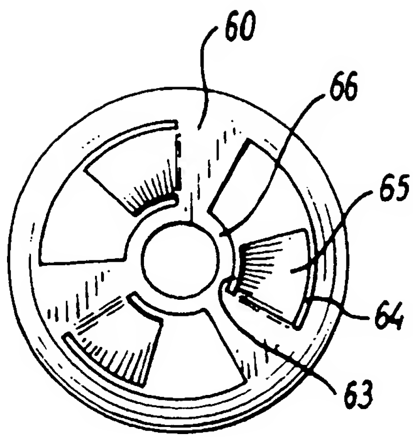


FIG. 13

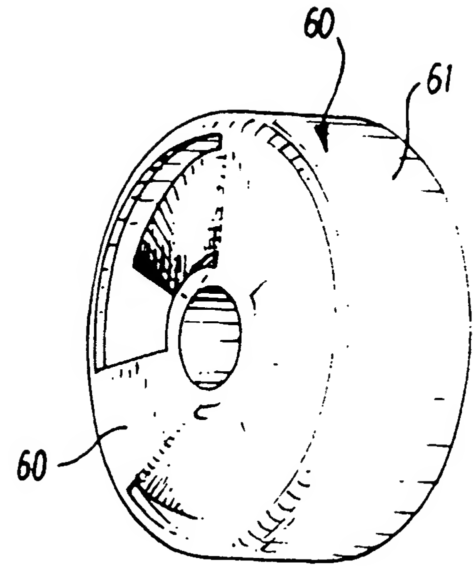


FIG. 13A

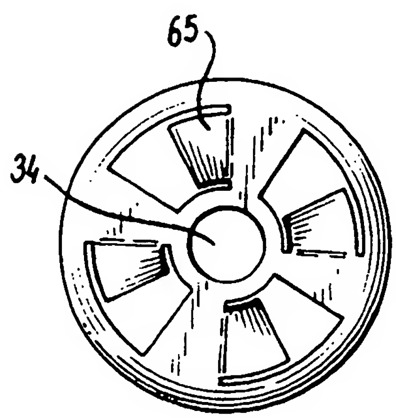


FIG. 14

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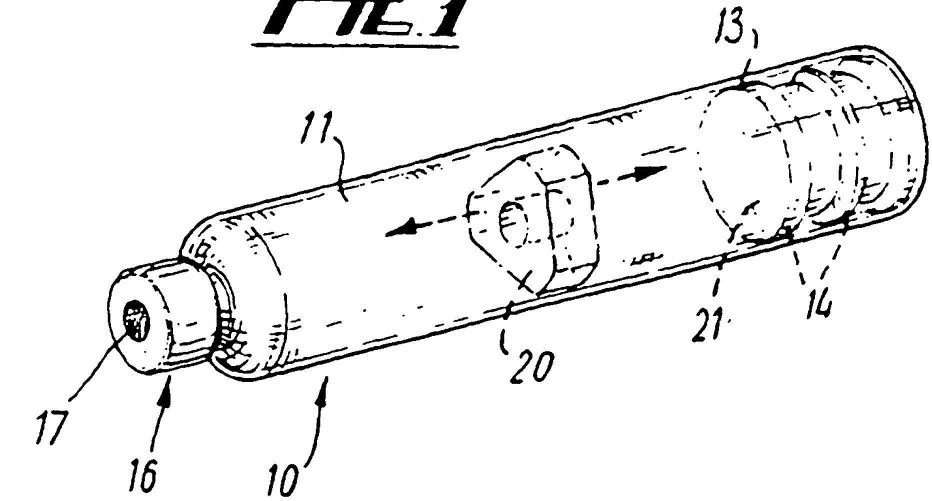
FIG.1



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